Greater Manchester Mental Health
NHS Foundation Trust

Cognitive behavioural therapy in comparison to treatment as usual in young adults at high risk of developing bipolar disorder (Bipolar At Risk): A randomised controlled trial to investigate the efficacy of a treatment approach targeted at key appraisal change: Bipolar At Risk Trial II (BART II) [Short Title]

REFERENCE INFORMATION / NUMBERS

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This protocol has regard for the Health Research Authority (HRA) guidance and order of content

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature:
.....

Date:
...../...../.....

Name (please print):
.....

Position:
.....

Chief Investigator:

Signature:
.....

Date:
...../...../.....

Name: (please print):
.....

(Optional)

Statistician:

Signature:
.....

Name: (please print):
.....

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	Dr. Thomas Richardson (clinician) Room 4065, Building 44 (Shakleton) Highfield Campus University of Southampton T.H.Richardson@soton.ac.uk Mr. Tim Rawcliffe (Lived experience) 465 Manchester Road Baxenden Accrington, Lancs BB5 2QF timraw@msn.com **Data Monitoring Committee** Professor Richard Morriss (Chair) Room C20 Institute of Mental Health Jubilee Campus Wollaton Road Nottingham NG8 1BB 0115 823 1289 Richard.Morriss@nottingham.ac.uk Dr. Rebecca Kelly (Clinician) PICuP Clinic, PO79 Clinical Treatment Centre Maudsley Hospital Denmark Hill London SE5 8AZ Rebecca.Kelly@slam.nhs.uk Dr. Theophile Bigirumarame (Statistician) Biostatistics Research Group Population Health Sciences Institute 4th Floor Ridley Building 1 Queen Victoria Road Newcastle upon Tyne NE1 7RU theophile.bigirumarame@newcastle.ac.uk

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ii. LIST OF ABBREVIATIONS

Define all unusual or 'technical' terms related to the trial.

List of Abbreviations	
AE	Adverse Event
BAR	Bipolar At Risk
BC	Behaviour Checklist
BD	Bipolar Disorder
BDI	Beck Depression Inventory
CAMHS	Child and Adolescent Mental Health Services
CBT	Cognitive Behavioural Therapy
CBT_{BAR}	Cognitive Behaviour Therapy for Bipolar At Risk
CCA	Complete Case Analysis
CI	Chief Investigator
CMHT	Community Mental Health Team
CRF	Case Report Form
CRN	Clinical Research Network
CTU	Clinical Trials Unit
CYPMHS	Children and Young People's Mental Health Service
EDIT	Early Detection and Intervention Team
EI (T)	Early Intervention (Team)
EQ-5D	European Quality of Life – 5 Domain
GAF	Global Assessment in Functioning
HAPPI	Hypomanic Attitudes and Positive Predictions Inventory
HRA	Health Research Authority
HTA	Health Technology Assessment
IAPT	Improving Access to Psychological Therapies
ICM	Integrative Cognitive Model
DMEC	Data Monitoring and Ethics Committee
EME	Efficacy and Mechanism Evaluation (EME) programme
FU	Follow-up
GCP	Good Clinical Practice
GMMH	Greater Manchester Mental Health NHS Foundation Trust

IMD	Index of Multiple Deprivation
LIFE	Longitudinal Interval Follow-Up Evaluation
LSOA	Lower Layer Super Output Areas
MCID	Minimal Clinically Important Difference
MRC	Medical Research Council
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
PPI	Patient and Public Involvement
PSR	Psychiatric Status Ratings
RA	Research Assistant
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture
RfPB	Research for Patient Benefit
SCID	Structured Clinical Interview for DSM-IV
SAE	Serious Adverse Events
SES	Standardised Effect Size
SOP	Standard Operating Procedures
SU	Service User
SURG	Service User Reference Group
TAU	Treatment As Usual
TFA	Theoretical Framework of Acceptability
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
WHOQOL	World Health Organisation Quality of Life
YMHRU	Youth Mental Health Research Unit

iii. TRIAL SUMMARY

Trial Title	Cognitive behavioural therapy in comparison to treatment as usual in young adults at high risk of developing bipolar disorder (Bipolar At Risk): A randomised controlled trial to investigate the efficacy of a treatment approach targeted at key appraisal change (BART II)
Internal ref. no. (or short title)	(BART II)
Trial Design	Our trial will be a multicentre, rater -blinded randomised control trial (RCT) with 2 parallel arms. It will compare a psychological intervention (Cognitive Behavioural Therapy for Bipolar At Risk (CBT_{BAR})) + Treatment As Usual (TAU) (treatment condition) **to** TAU alone (control condition). Outcome and mediational variables will be collected at baseline, 17-weeks, 27-weeks (after therapy cessation), and at 52-weeks. The primary outcome is mood swing symptom severity assessed by SCID-5 + Psychiatric Status Ratings/PSR's (SCID Longitudinal Follow-Up Evaluation (LIFE)) [1] at 27-week (post treatment) as measured by the PSR scores as an average of the prior 4 weeks. A longitudinal severity rating of overall symptom levels for each week over the time period (prior 4 weeks) is completed providing two LIFE scores, one for mania and one for depression [1]. Up to 26 individual weekly therapy sessions of up to 60 mins will be offered within a 26-week treatment window. Participants will be randomised to one of two trial arms. Randomisation will be independent and concealed, using permuted stratified blocks where site (5-levels) and BAR group (3-levels) are the stratification factors. It will be conducted via a web-based system conducted within York Clinical Trials Unit (CTU). Conducted in community-based NHS in 5 sites in the UK (representing 4 NHS commissioning regions in England): Greater Manchester, Lancashire, Sheffield, Birmingham, and Norfolk & Suffolk. The research objective is to recruit 338 participants across these 5 NHS sites in England who meet the Bipolar At Risk (BAR) criteria.
Trial Participants	The study population are young people meeting BAR criteria. The inclusion criteria are: - 16-25 years old - Meet criteria for one of the following: • **Group I**: Sub-threshold mania: elevated/expansive/irritable mood + ≥ 2 criteria from the mood module list for at least 2 consecutive days) • **Group II**: Depression + Cyclothymic features:

	mild depressive symptoms + diagnosis of cyclothymic disorder or bipolar disorder NOS as assessed by SCID-5 • **Group III**: Depression + genetic risk: mild depressive symptoms (Group 1) + genetic risk (first degree relative with bipolar disorder). - Help seeking - Provision of written informed consent **Please note, the BAR criteria above has been summarised. Please see fully explained criteria in Section 4 / Inclusion Criteria*
Planned Sample Size	338 participants
Treatment duration	Up to 26 weeks
Follow up duration	52-weeks
Planned Trial Period	April 2022 – March 2026 (48 months)

	Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure**
Primary Outcome	Mood swing symptom severity	SCID-5 assessment + PSR scores (SCID LIFE)	At 27-week timepoint, average over prior 4 weeks
Secondary Outcomes Appraisals of and responses to mood (hypothesised mechanisms)	To determine the impact of the CBT_{BAR}: Proposed mechanism of appraisals of internal state Ascent / descent behaviours	- Internal States Scale (ISS) - Hypomanic Positive Predictions Inventory (HAPPI) - Behaviours Checklist (BC)	Baseline, 17-weeks, 27-weeks, & 52-weeks
Mood Swings	On mood swing experiences for the following sub-categories: - 27-week and 52-week FU of time to transition to (hypo)mania - % of time in subthreshold symptoms - Time in symptoms (% of overall time & number of weeks during FU intervals) - Time to recovery from subthreshold (BAR) symptoms	- SCID LIFE (SCID-5 assessment (Modules A, B, C & D) + PSR scores) - Young Mania Rating Scale (YMRS) - Beck Depression Inventory (BDI) - Altman Self Rating Mania Scale	Baseline, 27-weeks, and 52-weeks

Health Utility	Healthcare costs: Service Use (including health & social care use & informal care)	- Service Use Interview - EQ-5D - Recovering Quality of Life (ReQoL)	Baseline, 27-weeks, and 52-weeks
Functioning	Functioning & Quality of Life:	- Global Assessment of Functioning (GAF) - Social & Occupational Functioning Assessment Scale (SOFAS) - World Health Organisation Quality of Life (WHOQoL)	Baseline, 27-weeks, and 52-weeks
Additional Secondary Outcomes	Sleep	- Pittsburgh Sleep Quality Index (PSQI) - Positive and Negative Sleep Appraisal Measure (PANSAM)	Baseline, 27-weeks, and 52-weeks
	Metacognition	- Metacognitions Questionnaire – 30 (MCQ-30) - Desire Thinking Questionnaire (DTQ)	Baseline, 27-weeks, and 52-weeks
	Response Style	- Response Style Questionnaire (RSQ)	Baseline, 27-weeks, and 52-weeks
	Schema	- Brief Core Schema Scale (BCSS)	Baseline, 27-weeks, and 52-weeks
	Substance Use	- SCID-5 (substance use disorders / Module E)	Baseline
	Anxiety diagnoses	- SCID-5 (Anxiety Modules F & G)	Baseline
	Feeding & Eating Disorders	- SCID-5 (Feeding & Eating Disorders / Module I)	Baseline
	Trauma & Stress related diagnoses	- SCID-5 (Trauma & Stressor-Related Disorders / L & K Modules)	Baseline
	Body Dysmorphic Disorder		Baseline

	Sleep Wake Disorders	- SCID-5 / Body Dysmorphic Disorder / Module Optional Disorders) - SCID 5 / Sleep Wake Disorders / Module Optional Disorders)	Baseline
Alliance Measurements	Therapeutic Alliance Research Assistant Alliance	California Psychotherapy Alliance Scales (CALPAS) – *Patient Version* California Psychotherapy Alliance Scales (CALPAS) *Therapist Version* Facilitative Alliance Measure (FAM)	Following CBT_{BAR} sessions 4 & 10 Following Baseline, 27-weeks, and 52-weeks
Qualitative sub-study	Participants' perceptions of how CBT_{BAR} effects psychologically driven appraisals and subsequent behaviours that control mood in the pathway to high and low mood states.	Qualitative interviews	Post therapy (after 26-weeks)

Investigational treatment	CBT_{BAR}
Formulation, Dose, Administration	Trial therapist delivering CBT_{BAR} in a 26-week treatment envelope allowing up to 26 sessions as follows: ▪ Mood continuum work ▪ Problem list generation ▪ Goal setting ▪ Idiosyncratic formulation (maintenance and longitudinal) derived from model ▪ In session measurement of appraisals and behaviour ▪ Cognitive strategies to target key appraisals of mood: advantages / disadvantages; developing alternative explanations; evidential analysis; surveys; cognitive processes; beliefs of self, world and other. ▪ Behavioural strategies: behavioural experiments; behavioural analysis including intended mood management Sessions offered face to face, but also offer flexible appointments via video calls (using NHS trust approved platforms such as TEAMS).

iv. FUNDING & SUPPORT IN KIND

Names and contact details of ALL organisations providing funding and/or support in kind for this trial	**FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN**
FUNDER National Institute for Health Research Evaluation, Trials & Studies Coordinating Centre University of Southampton Alpha House, Enterprise Road Southampton SO16 7NS http://www.nihr.ac.uk/	£2,167,119.40
SPONSOR Sarah Leo Head of Research & Innovation Greater Manchester Mental Health NHS Foundation Trust Tel: 0161 271 0076 Mob: 07342 068 227 E-mail: Sarah.Leo@gmmh.nhs.uk Addresses: Research & Innovation Office 1st Floor, Harrop House Bury New Road Prestwich Manchester M25 3BL 3rd Floor, Rawnsley Building Hathersage Road Manchester M13 9WL	See below for non-financial support provided

v. ROLE OF TRIAL SPONSOR, FUNDER, & RESEARCH SITES

SPONSOR

Greater Manchester Mental Health NHS Foundation Trust is the primary sponsor. The sponsor is the employer of the Chief Investigator (Dr. Sophie Parker). As the sponsor, GMMH will take an overall responsibility for proportionate and effective arrangements being set up to run and report this trial (as laid out by the HRA: UK Policy Framework for Health and Social Care Research - Health Research Authority (hra.nhs.uk). This includes:

- Reviewing the planned research and protocol and ensuring it: 1) takes into account relevant existing research evidence; 2) makes appropriate use of Patient, Service User, and Public Involvement (PPI); 3) is scientifically sound; 4) and is safe, ethical and feasible for the duration of the research.

- Ensuring the investigators, research team and research sites are suitable
- Ensuring the roles & responsibilities of the parties involved in the research and any delegation by the sponsor of its tasks are agreed and documented.
- Ensuring adequate provision is made for insurance or indemnity to cover liabilities that may arise in relation to the design, management and conduct of the research
- Ensuring appropriate arrangements are made for making information about the research publicly available before it starts
- Agreeing appropriate arrangements for making data accessible, with adequate consent and privacy safeguards, in a timely manner after it has finished
- Ensuring arrangements for information about the findings of the research to be made available including, where appropriate, to participants
- Ensuring that the research has approval from a Research Ethics Committee (REC)
- Verifying regulatory and practical arrangements are in place before permitting the research to begin in a safe and timely manner.
- Putting and keeping in place arrangements for adequate finance and management of the research project, including its competent risk management and data management.
- Ensuring that effective procedures and arrangements are kept in place and adhered to for reporting e.g. progress reports, safety reports, and for monitoring the research, including its conduct and the ongoing suitability of the approved protocol in light of adverse events or other developments.
-

FUNDER

This project (NIHR132622) is funded by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership. The views expressed in this publication are those of the author(s) and not necessarily those of the MRC, NIHR, or the Department of Health & Social Care.

The funder is responsible for (as taken from HRA: UK Policy Framework for Health and Social Care Research - Health Research Authority (hra.nhs.uk)

- Assessing the scientific quality, the relevance of the research to the target population, and the value for money of the research as proposed, involving patients, service users and the public.
- Reviewing information about the attribution of costs to confirm that costs to all parties (including excess treatment costs) have been identified and described in accordance with national guidance, and that the costs are not disproportionate compared to the value of the output.
- Considering whether the research is really achievable within the settings as a whole in which it is intended to be carried out, particularly in view of the priorities and constraints in health and social care if the research will have an impact on care provision
- Making ongoing funding conditional on a sponsor and relevant approvals being in place before the research begins (but not before initial funding is released, as some funding may be needed in order to put these in place)
- Using contracts and conditions of funding to promote compliance with this policy framework.

RESEARCH SITES

Research sites are the organisations with day-to-day responsibility for the locations where a research project is carried out. Research sites are responsible for the following:

- Demonstrate to the relevant approval bodies & sponsor that the location is suitable for the research as required to confirm capacity and capability
- Be aware of all research activity being undertaken on or through the site
- Ensuring that the roles & responsibilities of individuals at the site and any collaborating parties are agreed and documented for individual research projects
- Satisfying themselves that the research has approval from a REC and any other relevant approval bodies before research participants take part (including indirectly).

- The site must have access to a Health and Care Professional Council (HCPC) registered practitioner psychologist (Clinical, Health or Counselling Psychologist) and/or a UKCP registered psychotherapist who can be trained to deliver the CBT component
- Capture and report any AE/SAEs

vi. ROLES & RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITTEES / GROUPS & INDIVIDUALS

TRIAL MANAGEMENT GROUP (TMG)

The Trial Management Group (TMG) will comprise the following colleagues: CI (Sophie Parker), Lead Site Trial Managers (Lydia Pearson and Rebekah Carney), York Clinical Trials Unit (CTU) Deputy Director (Catherine Hewitt), York CTU Research Fellow (Jude Watson), York CTU Trial Manager (Lesley Sinclair), York CTU Trial Coordinator (Rachel Ellison), York CTU Trial Statisticians (Elizabeth Coleman, Catherine Hewitt), Trial Health Economist (Gemma Shields), site leads (Richard Bentall, Steve Jones, Matthew Broome, Tim Clarke, and Jon Wilson), qualitative supervisor (Sarah Peters), PPI lead (Heather Law), service user researcher (Wendy Jones), service user representative (Anton Strong), family/carer consultant (David Shiers), and additional collaborator (Dr. Chris Sutton).

The TMG will meet on a monthly basis and meeting minutes will be stored in the Trial Master File (TMF). The roles and responsibilities of the TMG include:

- Input into and comment on the protocol and other trial documentation at the start of the trial and throughout the duration of the trial should amendments be required
- Input into the development of the statistical analysis plan
- Nominating and inviting of members to join a TSC and DMC
- Involvement in the day to day running of the trial by supporting the CI and Trial Manager/ Co-ordinator
- Input into monitoring the progress of the trial, adherence to the protocol, patient safety and the accumulation of new information/ evidence of relevance to the trial
- Input into reviewing of serious adverse events where required and appropriate
- Input into Trial Steering Committee (TSC), Data Monitoring and Ethics Committee (DMEC) and funders meetings where required and assist with responses to any issues or concerns these groups may raise
- Promoting the trial

TRIAL STEERING COMMITTEE (TSC)

We will set up a Trial Steering Committee (TSC) prior to commencement of the research activity. The role of the TSC, as outlined by the NIHR (Research Governance Guidelines (nihr.ac.uk), is to provide overall supervision for a project on behalf of the Project's Sponsor and Funder and to ensure that it is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice.

The TSC will comprise an independent chair (Professor Kim Wright), independent statistician (Professor Richard Emsley), independent public member (Mr. Tim Rawcliffe), and independent clinician (Dr. Thomas Richardson). The chair will decide on additional members (up to 1 additional voting member to ensure 75% independence is maintained). The chair will also decide the observers that can be invited. These additional members / observers can include (but are not limited to) the BART II Chief Investigator (SPa), lead site trial manager (LP), trial statisticians (Catherine Hewitt or Elizabeth Coleman), colleague from the NIHR (Zoe Mitchell) and sponsor representative (Sue Dobson).

Meeting initially for approval of the protocol and standard operating procedures before the trial begins and twice yearly thereafter to monitor/supervise progress, consider reports and recommendations and any other factors that might compromise the progress and satisfactory completion of the trial. The TSC meetings will be scheduled to follow shortly after the Data Monitoring and Ethics Committee (DMEC) meetings so that reports from that group can be considered. Meetings of the TSC minutes will be stored in the TMF.

DATA MONITORING AND ETHICS COMMITTEE (DMEC)

We will set up a DMEC prior to commencement of the research activity. The DMEC will be a group of experts external to the study that will review accumulating data to ensure that for the participants there is no unavoidable increased risk for harm whilst answering the scientific question. The responsibilities of the DMEC have been taken from the following source: https://www.nihr.ac.uk/documents/research-governance-guidelines/12154.

The DMEC will monitor: 1) recruitment of study participants; 2) ethical issues of consent; 3) quality of data (including missing data); 4) the incidence of adverse events, and 5) any other factors that might compromise the progress and satisfactory completion of the trial.

The DMEC will comprise the independent chair (Professor Richard Morriss), independent clinician (Dr. Rebecca Kelly), and independent statistician (Dr. Theophile Bigirumarame).

vii. PROTOCOL CONTRIBUTORS

We have a track record of successful CBT trials and for those at high risk of BD (SPa, HL, WJ, SPe) and psychosis (SPa, HL, RB, TC, JW), as well as BD (SJ). Members of the research team have: developed cognitive behavioural models of and treatments for BD (SJ, RB, SPa); been involved in training courses for professionals in CBT (SPa, SJ) and leading on the national NHS programme for assessment of at risk mental states (SPa); assessment of BAR and those at risk of developing psychosis (SP, RB, SJ, LP, HL, MB, RC); been members of NICE Guideline Development Groups (SJ, DS) and one member who is a carer/parent (DS).

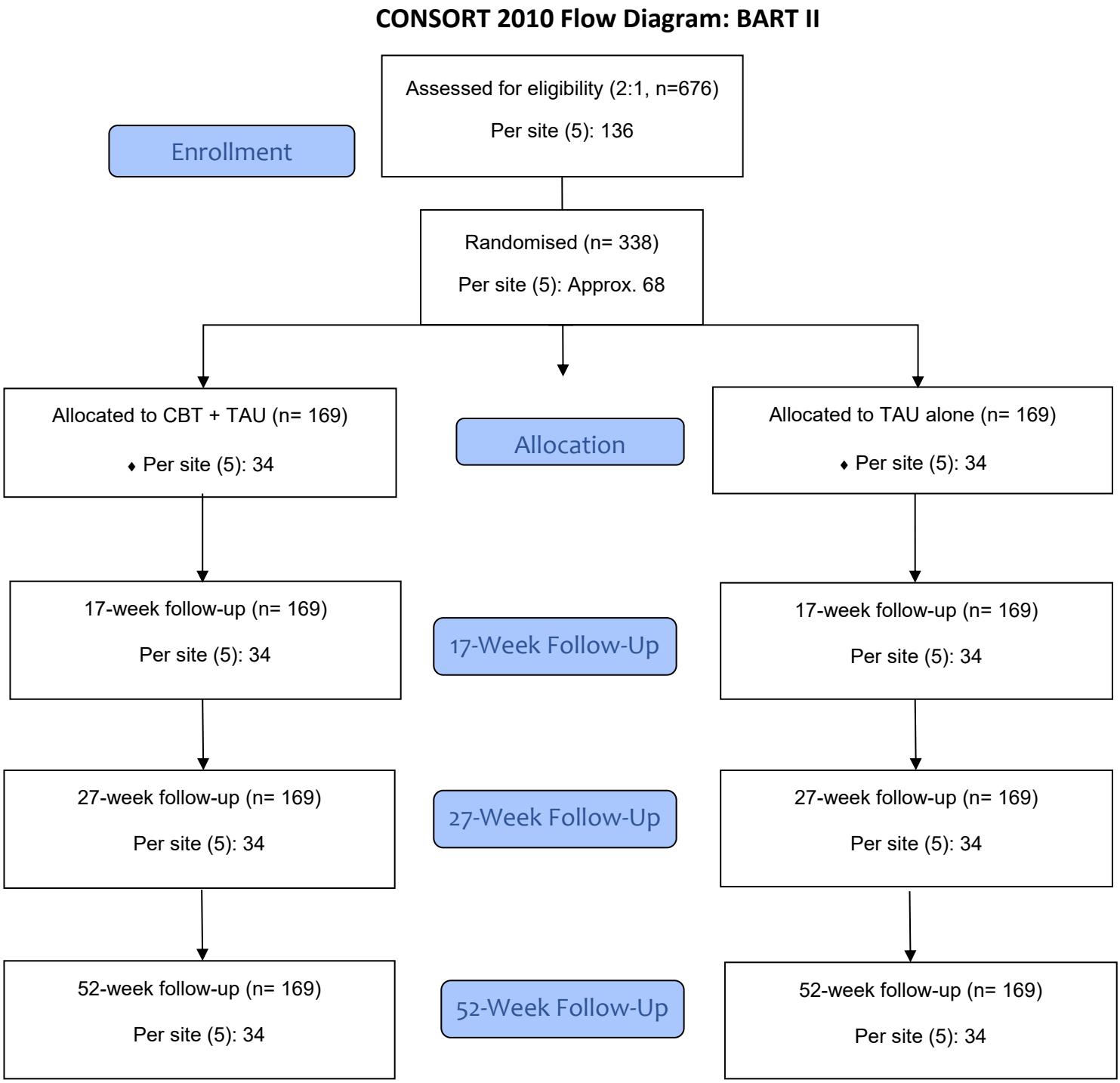
Co-applicants also have personal experience of mood swings and/or CBT within early intervention (AS, WJ); with expertise in service user (SU) involvement in RCTs (HL) and more specifically in BD (SJ) as a co-director of SPECTRUM centre for bipolar disorders. We have strong links with national training organisations, NICE, Royal Colleges, and NHS services with successful implementation of evidence-based practice including in Early Intervention (EI) and Children and Young People Mental Health Services (CYPMHS). The team has strong expertise in trial management (HL, RC) design and analysis (CH, CS), as well as CTU involvement (CH, JWa, LS, RE, IC) expertise in health economics evaluations of mental health interventions (GS) and SPe is an internationally and nationally recognised expert in qualitative methodologies as applied to mental health. All site leads (TC, JW, SJ, RB, MB) are clinicians with expertise in youth models, BD, SMI and psychological models (including mechanisms) in service delivery and/or research.

PPI will be led by HL, highly experienced at leading PPI work in research settings and across multiple population groups e.g. psychosis, at risk mental states (ARMS), and with young people. Funded to lead on this work, HL will work collaboratively with service user and carer co-applicants to deliver this strand of the research in line with our objectives, for example, co-facilitating Service User Reference Groups (SURGs) with someone with lived experience.

viii. KEYWORDS

1. Bipolar Disorder 2. Bipolar At Risk 3. Prevention 4. Cognitive Behavioural Therapy
5. Appraisal Change 6. Youth Mental Health

ix. TRIAL FLOW CHART



1. BACKGROUND & RATIONALE

EXPLANATION OF THE HEALTH PROBLEM TO BE ADDRESSED

Bipolar Disorder (BD) is the World's 18th and Western Europe's 17th greatest cause of years lived with disability [2], rising for young people to the 3rd (female 15-19y) and 7th (male 20-24y) cause of disability adjusted life years [3]. The World Health Organisation states BD is a major cause of loss of life/health in 15-44 year olds [3]. BD has the highest suicide rate of all psychiatric diagnoses [4] increasing risk above the general population by 20-30 times [5]. Young people in early stages of BD are at highest risk [6]. BD has consequences for individuals, families and society. Affecting 1-3% of the population [7, 8], it costs £5.2bn per year, including NHS costs and lost employment, projected to rise to £8.2bn per year by 2026 [9]. With an average duration of untreated illness (DUI) of 6-10 years [10], people with adolescent onset have prolonged DUI [11]. Long DUI is linked with more mood episodes and higher risks of suicide [12].

The James Lind Alliance identified priorities for those with BD including rapid access to diagnostic assessments, developing effective talking therapies including CBT and individually tailored treatments [13]. Youth service models propose to widen intake criteria to encompass BD, and those at risk of developing BD, with the aim of reducing symptoms and risk of progression to more severe illness [14]. Early Intervention (EI) in Psychosis services show health and economic benefits [15]. Our trial will provide data for expansion into BD including which mechanisms are effective treatment targets in reduction of risk for long-term distressing mood swings. Extending EI to include BD could yield £25m savings in the UK, increasing by £4m if including early detection [16]; those meeting bipolar at-risk criteria (BAR) [17, 18], and who are help seeking, distressed NHS patients.

Early detection of BD has focused on familial risk [19-21] and identification of state-trait factors [14]. Detection of those at risk for BD is possible using standardised criteria [17, 18]. Bipolar at-risk criteria (BAR) consists of youth (16-25) experiencing distressing high mood; and/or high and low mood swings; and/or a first degree relative with BD plus depressed mood. This has predictive validity, can be reliably assessed (in a NHS context), holds clinical utility and is suitable for numbers needed to screen [10]. Most people meeting BAR criteria present with depressed mood (often atypical depression [22]) and mood swings which are poorly recognised and misdiagnosed. This leads to inappropriate treatments e.g. antidepressants which can induce mania [23], or psychological treatments for unipolar depression that do not target modifiable risk factors such as atypical depression or mood swings. Reviews emphasise a clinical staging model to identify and treat BAR individuals [24]. Early detection of BD could reduce hospitalisation and increase functioning [25]. BAR individuals are 100 times more likely to convert to first-episode mania than the general population, and 20 times more likely than those with unipolar depression [6, 26, 27], representing a unique chance to intervene.

THE KNOWLEDGE GAP THIS RESEARCH WILL ADDRESS

Minimal evidence exists about effective treatment options for those meeting BAR criteria. NICE guidelines recommend offering people with BD psychological interventions (CBT) [28]. For children and young people, pharmacological treatment is only offered when symptoms are severe [28]. Treatment access is difficult and lengthy. DUI is linked with poor outcome [29] although treatments can be delivered with beneficial effects in routine services [30]. Meta-analyses report the efficacy of CBT to cut relapse and improve symptoms of depression, mania, and functioning in BD [31-35] and that it is cost-effective when compared with TAU [36]. A recent RCT found CBT significantly improved outcomes in recent onset BD [37], and studies of psychological therapies for young people with BD report benefits of CBT [38]. NICE do not recommend CBT as a treatment for BAR individuals due to no consensus regarding early screening and lack of quality trials [28]. A rigorous RCT is needed to evaluate CBT's efficacy to reduce distressing mood swings and understand to what extent CBT reduces mechanisms central to a model of mood swings [39].

A literature search was conducted (10.11.2020) on the platform OVID for AMED, PSYCHinfo, Cochrane [AII], Medline, Embase, CINAHL with the terms "Bipolar At-Risk", "First-episode", "Hypomania", "Cyclothymia",

"Familial Risk", "Psychological therapy", and "Psychological Intervention". Studies focused on interventions for BD, with minimal research into BAR. A review assessing pharmacological interventions for BAR found a lack of high-quality research on preventative treatments [40], so could not conclude whether pharmacological approaches are beneficial or harmful. Coupled with potential safety considerations, psychological interventions might have an advantage over pharmacological interventions [41]. An evidence map of psychosocial interventions for the earliest stages of BD [42] included those at high risk. It reported 5 completed studies (three case series and two RCTs) linked with 4 publications [43-46]. Our search found two further small case series, one of which was published [47]. Trials of psychosocial interventions [43-47] were small and underpowered and some non-randomised.

A more recent review of clinical trials for people at high risk of developing BD highlighted an additional three RCT's [48-50] assessing psychological therapies with this group however all are small and underpowered. These therapies include a family focused therapy, Interpersonal and Social Rhythm Therapy (IPSRT) and CBT. Family focused therapy showed reduced mood trajectories compared with psychoeducation (47) whereas the IPSRT study (48) did not show a self-reported mood differences between the treatment and non-treatment groups. The most relevant study is Leopold et al. [50] who investigated CBT based on a cognitive psychoeducational therapy for BD [51] compared to unstructured group meetings with BAR. Both participant groups benefited in affective symptomology and psychosocial functioning, thus it was highlighted the psychotherapeutic interaction required clarification. Finally, a trial of GROUP-CBT for BAR is ongoing in Germany [52] but is underpowered (target n=100) to understand efficacy and is not exploring mechanisms associated with effects.

WHY IS THIS RESEARCH NEEDED NOW?

Bipolar disorder is a high cost mental health problem (£5.2bn per year) and with cost projections of £8.2bn per year by 2026 [9] opportunities to intervene earlier need to be pursued. The costs to young people and their families can be vast with BD ranked as the 3rd (female 15-19y) and 7th (male 20-24y) greatest cause of disability adjusted life years and described by the World Health Organisation as a major cause of loss of life/health in 15-44 year olds [3]. Improving the mental health of children and young people (0-25) is a major government priority with the commitment that more children and young people under 25 will have access to evidence based treatments through NHS services or school/college mental health support teams by 2023 to 2024 [53]. This sits alongside the commitment to reduce the loss of life to suicide in the UK. Research has shown BD to have the highest suicide rate of all psychiatric diagnoses [4] with young people in early stages of BD being at highest risk [6]. In order for the government to meet the targets for the NHS Mental Health Implementation Plan [54] and to achieve its vision for parity of esteem between mental and physical health for people of all ages new evidence based treatments are required.

It is imperative that research is undertaken now as services are seeking to understand how to expand youth service models to widen intake criteria to encompass BD, and those at risk of developing BD, in the aim of reducing symptoms and risk of progression to more severe illness [14]. There is potential for significant savings [9] and data demonstrating health and economic benefits of Early Intervention (EI) services [15] and then to train the growing CYPMHS workforce. Our trial will provide data for expansion of EI for BD including which mechanisms are effective treatment targets in reduction of risk to long-term distressing mood swings.

HOW WILL THIS RESEARCH LEAD TO AN IMPROVEMENT IN THE CARE OF THE PATIENT POPULATION?

Data from our RfPB trial showed that our BAR participants were help-seeking, distressed NHS patients, frequently with complex and co-morbid difficulties, who were in need of specialist intervention. The modal range of SCID-IV diagnoses met by our participants was 2-3 (48.7%: *N*= 37) although a substantial proportion met criteria for ≥6 (25%: *N*= 19). Anxiety was a prevalent difficulty for our participants. Most (73.4%) of our sample met criteria for at least one anxiety disorder at baseline, and many participants had multiple comorbid anxiety disorders according to the SCID-IV assessment; 24.7% of our sample met criteria for 2-3, and 24.7% for

≥4. Almost ⅔ of participants (59.2%: *N*= 45) had attempted suicide at least once and the average BDI-II score (37.9) indicated that participants on average met criteria for severe depression.

Additionally, almost all participants (94.7%: *N*= 72) had previously sought mental health support from services. This data indicates that our BAR participants were distressed, help-seeking individuals with complex and comorbid difficulties comparable to those faced by people with BD [3, 5, 55, 56]. These findings are also similar to those reported by Bechdolf and colleagues [18] who reported similar levels of unemployment, suicide attempts and Axis-I anxiety disorders (experienced by 69.7% of the sample). The mean GAF score of 51.0 indicates that our participants were experiencing moderate levels of impairment in educational/occupational and social functioning. Participants' treatment pathways were notable, as they demonstrated the breadth of treatments and services that people had accessed for help. People reported having accessed an average of five services/interventions each. The range of services/interventions accessed was 1-10 and the modal number accessed was four. This suggests that many people had made multiple attempts at seeking support and still had significant needs on entry into the trial.

Almost all participants reported seeking help from their GP about their mood difficulties, with psychotropic medication as the second most common intervention people reported accessing, with antidepressant use particularly high (N=42; 55.2%). The high reported rates of access to CAMHS (N=36; 47.4%) and school/college counsellors (N=15; 19.7%) suggest that many participants' mental health difficulties had begun early in life. Almost a third of participants (N=25) had sought treatment through primary care psychology/IAPT. It is also notable that there were relatively high rates of access to services for psychiatric emergencies: 18.4% (N=14) of participants reported accessing A&E / RAID teams at least once, 9.2% (N=7) home-based treatment/crisis teams, and 10.5% (N=8) inpatient admissions to mental health wards. This indicates frequent occasions of extreme distress and crisis experienced by our participants. These figures reflect the lack of effective treatments for distressing mood swings for those meeting BAR criteria and are consistent with findings that people with BD either go untreated for many years or receive NHS treatment in early stages which does not meet their needs. It must be noted that this was a single-site study completed in Greater Manchester; considered a large and diverse city but nonetheless it cannot be assumed that the characteristics of all BAR individuals are the same. A larger, multi-site RCT will be important to expand the evidence base of effective treatments for these NHS patients. We would anticipate our research could to lead to important developments within the NICE guidelines for Bipolar Disorder (CG185) similar to the recognition and management of those at risk of developing psychosis within the NICE guidelines for Psychosis and Schizophrenia (CG178; CG155).

PROOF OF CONCEPT

Psychotherapy research should be based on theoretical models of BD to know the mechanisms involved clarifying aspects of therapy suited to phases of the disorder. Treatments are potentially more effective when targeting mechanisms that confer risk to maintaining/escalating mood swings. In our pilot study, we applied a CBT intervention based on one such scientifically grounded theoretical model of mood swings [57]. CBT_{BAR} intervention components broadly fall under three categories of core principles and values (building trusting relationships, validation and normalising of experiences, collaborative goal setting), cognitive change strategies targeting appraisals and behavioural strategies modifying unhelpful coping responses. Proposed specific mediators of change include: (1) extreme appraisals of mood states (2) unhelpful coping behaviours. Intermediate outcomes include reduced mood swings and distress regarding mood states. Longer term potential benefits of the CBT_{BAR} intervention include service user benefit (improved recovery and quality of life, reduced transition to bipolar disorder) and service improvement (skilled workforce, a replicable model, inclusion of BD within EI and prevention services). Our feasibility trial demonstrated excellent acceptability/feasibility data with promising results highlighting those randomised to CBT_{BAR} significantly improved compared to those who received treatment as usual (TAU) across measures at the 27- and 52-week follow-up points, including mood [58] (report available here). In addition, qualitative interviews showed that trial randomisation and processes were acceptable and the CBT_{BAR} intervention brought about positive changes for participants [59]. An evaluation of efficacy is the next step for this research in line with MRC framework for developing complex interventions.

The proposed research aims to evaluate the efficacy of a specific intervention (CBT_{BAR}) in a 2-armed multicentre RCT comparing CBT_{BAR} plus TAU vs. TAU only for BAR individuals. We also aim to investigate how CBT_{BAR} impacts on the pathway between key psychological processes and mood swings.

2. OBJECTIVES & OUTCOME MEASURES / ENDPOINTS

OVERALL AIM

The overall aim is to conduct a two-arm multicentre, rater-blind, randomised controlled trial comparing CBT_{BAR} plus TAU vs. TAU only for BAR individuals to evaluate the efficacy of a specific intervention (CBT_{BAR}). We also aim to investigate how CBT_{BAR} impacts on the pathway between key psychological processes and mood swings. The overarching research questions are:

1) To what extent is CBT_{BAR} (a psychological therapy) effective in reducing distressing mood swings when compared to Treatment As Usual (TAU) for BAR individuals? *(Measured at 27-weeks follow-up)*

2) Investigate how CBT_{BAR} impacts on the pathway between key psychological processes and mood swings measured at 17-week follow-up.

3) What are the perceptions of patients and health care professionals regarding the implementation of this therapy in NHS services?

EFFICACY AIMS

The trial has a number of efficacy aims:

1) To determine the efficacy of CBT_{BAR} (a specifically developed psychological therapy) in reducing distressing high and low mood swings when delivered to patients meeting BAR criteria.

2) To determine whether positive effects of CBT_{BAR} last over a 52-week follow-up period.

3) To investigate patients', health care professionals, and NHS stakeholders' perceptions of implementation of CBT_{BAR}.

Primary Objective

To determine the efficacy of CBT_{BAR} (a specifically developed psychological therapy) in reducing distressing high and low mood swings when delivered to participants meeting BAR criteria.

Primary Outcome Measure/Endpoint

Mood swing symptom severity assessed by SCID-5 + PSR's (SCID LIFE) [1] at 27-week (post treatment) as measured by the PSR scores as an average of the prior 4 weeks. A longitudinal severity rating of overall symptom levels for each week over the time period (prior 4 weeks) is completed providing two LIFE scores, one for mania and one for depression [1].

Mechanism Objective

To investigate the extent to which CBT_{BAR} impacts on distressing high and low mood swings (SCID-5 + PSR's (SCID LIFE)) via extreme positive and negative appraisals of internal states (HAPPI) which then impacts on subsequent behaviours (BC) used to control mood (ISS).

Mechanism Measures/Endpoint

- 17-week (during therapy): Hypomanic Positive Predictions Inventory (HAPPI), the Behaviour Checklist (BC) and Internal States Scale (ISS)
- Participants' perceptions of how CBT_{BAR} effects psychologically driven appraisals and subsequent behaviours that control mood in the pathway to high and low mood states derived from qualitative interviews (after therapy cessation).

Secondary Objectives

To determine the efficacy of CBT_{BAR} in:

- reducing distressing high and low mood swings at 52-week follow-up period
- the likelihood of transition to BD in comparison to TAU alone over a 52-week follow-up time period
- the reduction of key problematic psychological processes over a 52-week follow-up period
- improved functioning and quality of life compared to TAU alone over a 52-week follow-up time period

Secondary Outcome Measurement/Endpoint

Mood Swings measured at 17-, 27-, and 52- week follow-up points:

- Psychiatric Rating Status scores (SCID LIFE) [1]):
    - Mood swing symptom at 52-week as measured as an average of the prior 4 weeks;
    - % of time in subthreshold symptoms;
    - residual or recovered time periods;
    - time in symptoms (% of overall time and no of weeks during follow-up intervals) [60, 61];
    - number of 'well' weeks as defined as weeks with none or minimal symptoms
- Structured Clinical Interview for Axis 1 Diagnoses (SCID- 5; [62]): Semi structured interview assessing mood diagnoses at 17-, 27- and 52-week follow up.
    - capturing time to transition to first episode (hypo)mania)
    - time to recovery from subthreshold (BAR) symptoms will also be captured over the 52-week follow-up period

Appraisals of and responses to mood (hypothesised mechanisms) measured at 17-, 27-, and 52- week follow-up points:

- Hypomanic Positive Predictions Inventory (HAPPI; [63]): a self-report measure assessing for multiple, extreme, and personalised appraisals about high and low mood at 27- and 52-week follow-up.
- Behaviour checklist (BC;[64]): a 21 item questionnaire of ascent, normalising and descent behaviours and internal states
- Internal State Scale (ISS; [65]): measuring the severity of mood states (self-report) at 27- and 52-week follow-up

Self-report mood swing questionnaires, measured at 27-, and 52- week follow-up points:

- Beck Depression Inventory (BDI-II; [66]): measuring the severity of depression (self-report) at 27- and 52-week follow-up.
- Young Mania Rating Scale (YMRS; [67]): semi-structured interview assessment of high mood at 27- and 52-week follow-up.
- Altman Self Rating Scale (ASRS; [68]): measuring high mood experiences (self-report) at 27- and 52-week follow-up.

Health Utility, measured at 27-, and 52-week follow-up points:

- Service Use Interview (adapted for this study): use of formal and informal health and social care at 27- and 52-week follow-up.
- Health Questionnaire (EQ-5D-5L; [69]): health status and health related utility scores of participants at 27- and 52-week follow-up.
- Recovering Quality of Life (ReQoL; [70]):

Functioning, measured at 27-, and 52- week follow-up points:

- Global Assessment of Functioning scale (GAF; [71]): measure of an individual's level of social, occupation and psychological functioning at 27- and 52-week follow-up.
- Social and Occupational Functioning Assessment Scale (SOFAS; [72]): Additional measure of an individual's level of social & occupational functioning at 27- and 52-week follow-up.
- World Health Organisation Quality of Life (WHOQOL-BREF; [73]): will be administered to assess quality of life.

Additional secondary outcomes, measured at 27-, and 52- week follow-up points:

- Pittsburgh Sleep Quality Inventory (PSQI; [74]): Measure quality of sleep at the 27- and 52-week follow-up.
- Positive and Negative Sleep Appraisal Measure (PANSAM;[75]): Measure appraisals of sleep across high and low mood states at the 27- and 52-week follow-up.
- Metacognition Questionnaire (MCQ-30;[76]): at 27- and 52-week follow-up
- Desire Thinking Questionnaire (DTQ; [77]): at 27- and 52-week follow-up
- Response Style Questionnaire (RSQ; [78]): at 27- and 52-week follow-up
- Brief Core Schema Scale (BCSS; [79]): at 27- and 52-week follow-up
- All additional treatments in both arms will be monitored using a service use interview and LIFE ratings of pharmacological and psychosocial treatments for all mental health contacts, frequency of sessions, length of treatment, and number of days of inpatient and partial hospitalisation. Medication usage and dosing are recorded on a weekly basis as important confounders.

Qualitative Objectives

To understand how participants experience or perceive the intervention to have impacted on their mood, behaviours and symptoms and draw patterns across participants' experiences.

To identify key themes associated with the implementation of CBT_{BAR} from the perspective of key stakeholders

Qualitative Measure/Endpoint

A qualitative topic guide (after the end of therapy, post 27-weeks will be employed to identify how participants experience or perceive the intervention to have impacted on their mood, behaviours and symptoms and draw patterns across participants' experiences. We will seek to identify components of the intervention that participants continued to utilise beyond therapy, and ways they have incorporated these into their lives.

A qualitative topic guide (after the end of therapy, post 27-weeks) for key stakeholders will be utilised to identify potential barriers and solutions to future implementation.

Hypotheses

Our outcome measures are designed to test the following hypotheses.

Efficacy Hypotheses

1) CBT_{BAR} + TAU will lead to improvement in mood swings (SCID-5 + PSR's (SCID LIFE)) compared to TAU alone at
    a. end of treatment (27-week follow-up)
    b. follow-up (52-week follow-up).

2) CBT_{BAR} + TAU will reduce the likelihood of transition to BD in comparison to TAU alone over a 52-week follow-up time period.

3) CBT_{BAR} + TAU will lead to improved functioning and quality of life compared to TAU alone over a 52-week follow-up time period.

Mechanistic Hypotheses

1) CBT_{BAR} + TAU will reduce extreme positive and negative appraisals of internal states (HAPPI) and subsequent behaviours used to control mood (BC) at 27 weeks.

2) The mechanism by which CBT_{BAR} causes improvement in mood swings (SCID-5 + PSR's (SCID LIFE)) is due to the reduction of extreme positive and negative appraisals of internal states (HAPPI) which in turn improves subsequent behaviours used to control mood (BC) and then internal states (ISS).

Internal Pilot Progression Criteria

An internal pilot will be conducted with a proposed length to month 16 (month 7 of recruitment). By month 16 (⅓ of the entire recruitment window, month 7 of the recruitment timeline) we plan to recruit ⅕ (68) of our total target (338), see table 1. This will be monitored by the trial management group and reviewed by the Trial Steering Committee as necessary

% / Threshold*	Red	Amber	Green
Trial recruitment	<60% of target (68) ≤40 recruited	60-99% of target (41-67) 41-67	≥100% ≥68
Recruitment rate/ site/ month	≤1.6	1.6-2.1	≥2.2
Number of sites opened	1-2	3-4	5
Proportion receiving allocated intervention	<90% (≤61)	90-94% (62-64)	≥95% (65)

Table 1. Internal pilot progression criteria at month 16 (month 7 of recruitment window) based upon recruiting 1/5 of total target (threshold = 68)*

3. TRIAL DESIGN

The design of the proposed main trial work has been developed with reference to CONSORT (http://www.equator-network.org/reporting-guidelines/consort/) and SPIRIT guidelines (http://www.spirit-statement.org/), and the TIDieR checklist and guide (http://www.bmj.com/content/348/bmj.g1687).

MAIN TRIAL

Our trial will be a multicentre rater-blinded (primary outcome) RCT with 2 parallel arms. It will compare a psychological intervention (CBT_{BAR}) + TAU (treatment condition) to TAU alone (control condition). The trial will recruit 338 participants who meet the Bipolar At Risk (BAR) criteria and randomly allocate them to a 6-month package of either condition.

Randomisation will be independent and concealed, using permuted stratified blocks, where site (5-levels) and BAR group (3-levels) are the stratification factors. It will be conducted via a web-based system conducted within York CTU. Assessors will be masked to allocated treatment. Masking will be maintained using a wide range of strategies (e.g. separate offices for therapists and researchers, protocols for answering phones, message taking and secretarial support, separate diaries and security for electronic randomisation information).

Assessor's blind and independent to treatment group will collect all outcome and mediational variables at baseline, 17-weeks (during treatment window capturing SCID-5 + PSR's (SCID LIFE), HAPPI, BC and ISS), 27-weeks (after therapy cessation), and at 52-weeks. Participants will receive £20 reimbursement upon completion at each assessment point as a thank you for their time.

The assessors will also contact people via phone at 39-weeks to promote retention in the trial. We will ask about general wellbeing since the last assessment (including documenting any potential serious adverse events), and any changes to contact details. Participants will receive a £5 supermarket voucher of their choice to thank them for their continued participation.

For those participants who are randomly selected to receive the CBT_{BAR}, they will be offered up to 26 individual weekly therapy sessions of up to 60 mins in length. These will be delivered by a Clinical Psychologist or psychological therapist.

NESTED QUALITATIVE WORK

In addition to the main trial, we will also be conducting qualitative interviews/focus groups to understand the perceived mechanisms of change for the participants offered the CBT_{BAR} (mechanistic objective), as well as the implementation of CBT_{BAR} in NHS services (implementation objective).

We will recruit two groups of up to 25 participants. The first group will be participants from the treatment arm across of 5 sites. The 2nd group will be key stakeholders including health professionals, service providers, commissioners, service providers/leads, clinicians, and service users.

Sampling will be purposive. For the implementation group we will be recruiting participants who received the CBT_{BAR}, their family members, and a mix of health professionals including those delivering the therapy, those who are experienced in delivering CBT, and commissioners. For the perceived mechanism of change group we will be recruiting participants who scored differently on the therapeutic alliance measure, who have varying mood experiences following the intervention (as measured by the SCID-5 + PSR's (SCID LIFE)), and who have varying change in their appraisals (as measured by the HAPPI). For both the implementation and perceived mechanism of change interviews with our service user participants, we will seek a diverse & inclusive sample (e.g. ethnicity, socioeconomic status, gender), level of engagement in therapy, and non-responders. We will be considering what services the BAR group of young people are currently accessing e.g. primary care and take into account the different service set ups across the multiple sites taking part in this trial.

Participants who take part in a qualitative interview/focus group will receive £20 reimbursement for their time.

Sample Size

Sample size: quantitative work

Whilst we plan to include LIFE depression and LIFE mania 4-week average PSR scores as co-primary outcomes, overall symptom severity of depression is greater compared with mania in this population, as is its standard deviation [80]. Although it may be argued that a minimally clinically important difference (MCID) in LIFE PSR mania score is somewhat smaller than the MCID for the PSR depression score, the relative difference will be smaller than that for the SD. This means that the Standardised Effect Size (SES) will be smaller for depression than that for mania and, therefore, that the sample size to detect the MCID will be greater for depressed mood

than for mania. On the LIFE PSR, our eligible population will score at the higher end of the subthreshold range (3-4) as those scoring 5-6 will confer research diagnostic criteria and therefore not meet the inclusion criteria for the trial; based on our pilot trial (mean baseline BDI-II score of 37.9), participants will tend to be towards the upper end of the subthreshold range (i.e. mean around 3.75). Button [81] reported that a MCID for the BDI-II is around 17-18%; given that we expected similar sensitivity for the mean LIFE depression PSR scores as would be the case for BDI-II, a difference of around 0.5 points (0.18*[3.75-1]=0.50 (to 2 d.p.)] on the PSR for LIFE depression in order to indicate that CBT_{BAR} is having an important effect.

To detect a between-group mean difference of 0.5 points (SD=1.3 points [80]) on the mean 4-week PSR for LIFE depression score at 27-weeks follow-up we require 286 participants with outcome data to achieve 90% power, using an ANCOVA (with 2.5% two-sided significance level), assuming a conservative correlation of 0.4 between baseline and 27-week scores [82]. Inflating the sample size to allow for a conservative 15% attrition (attrition was 13% in our feasibility trial, 57) requires a target to randomise of 338 participants (approx. 68 per site). This sample size will provide greater than 90% power to detect a rather more conservative MID on LIFE PSR for mania (e.g. equating to 98.5% to detect a target effect of 0.25 points [estimated within-group SD=0.5 points]) [80]. In each case, power will be increased due to the (multiple) correlation between outcome and the full set of explanatory variables adjusted for in the model. We have not allowed for a random therapist effect in our sample size calculation as the effect on depression outcome (BDI-II) in our pilot trial was 0, although the confidence interval was wide; we will, however, include the addition of a random therapist effect amongst our sensitivity analyses.

Assuming a standardised effect size of the intervention on the HAPPI of 0.4, 286 participants with mediator and primary outcome data will also allow for 88.5% power for estimation of an indirect effect of 40% via the putative primary mediator (HAPPI), or 83.5% power for the estimation of a 30% indirect effect, based on a total effect on the intervention of the MCID (i.e. 0.5) (with a 2.5% significance level, estimated using the R package medssp, based functions provided in Vittinghoff and Neilands [83]

Sample size: qualitative work

We will recruit two groups of 15-25 people each for individual interviews as part of the qualitative work: 1 group will be participants from the treatment arm of the trial across all 5 sites and 1 group will be comprised of key stakeholders including health professionals and service providers and commissioners. Sampling will be purposive, seeking to ensure maximum variance in the final sample and, seeking disconfirming cases where relevant. For the service user group we will ensure participants are drawn from across all 5 trial sites, and in order to build upon the acceptability work in the original BART trial will seek a more diverse and inclusive sample (e.g. ethnicity, socioeconomic status, gender) and level of engagement in therapy, including non-responders. The stakeholder groups will include health professionals involved in delivery of CBT_{BAR} and other interventions and services for this population, and referrers (and potential referrers) to the trial from a range of services and across geographical area.

4. PARTICIPANT ELIGIBLITY CRITERIA

MAIN TRIAL

Inclusion criteria

The study population are young people meeting BAR criteria. The inclusion criteria are:

- 16-25 years old
- Meet criteria for one of the following:
    - **Group I**: Sub-threshold mania:
        i. For at least 2 consecutive days but less than 7 days: period of abnormally and persistently elevated, expansive or irritable mood + at least 2 criteria from the list (≥ 3 for irritable mood):
            1. (1) inflated self-esteem/grandiosity, (2) decreased need for sleep, (3) more talkative than usual, (4) flight of ideas/racing thoughts, (5) distractibility, (6) increase goal directed activity or psychomotor agitation, (7) excessive involvement in activities that have a high potential for painful consequences.
    - **Group II**: Depression + Cyclothymic features:
        i. Depression (for at least 1 week): depressed mood / loss of interest or please + 2 criteria from the list:
            1. (1) significant weight loss, (2) insomnia or hypermania nearly every day, (3) psychomotor retardation/agitation, (4) fatigue/loss of energy, (5) feelings of worthlessness/excessive or inappropriate guilt, (6) diminished ability to think or concentrate, (7) recurrent thoughts of death/suicidal ideation

        PLUS

        ii. Cyclothymic features: numerous episodes with sub-threshold manic symptoms not meeting Group 1 criteria: subthreshold mania as defined in Group 1 for 4 hours within 24-hour period and at least 4 cumulative lifetime days in the past 12 months.

    - **Group III**: Depression + genetic risk:
        i. Depression (See Group 2)

        PLUS

        ii. Genetic risk: first degree relative with BD
- Help seeking
- Provision of written informed consent

Exclusion Criteria

- History of a treated/untreated manic episode or psychosis of 1-week duration or longer
- Treatment with a mood stabiliser for longer than 6-weeks or antipsychotic for 3-weeks [evidencing exclusion on point above or at the time of the assessment whereby at-risk status cannot be confirmed]
- Organic brain disorder
- Unable to complete assessments due to language barriers
- Inpatient/acute psychiatric care needed
- Primary substance abuse / dependency

NESTED QUALITATIVE STUDIES

All participants will be eligible to take part in the nested qualitative study. This also applies to their family / carers who they might refer to be invited to take part in the nested qualitative study. In addition, stakeholders

who come in to contact with young people that meet BAR criteria will also be considered as suitable for the nested qualitative interview. This could include university counselling staff, primary care psychology therapists, and psychiatrists working in the NHS.

5. TRIAL PROCEDURES

RECRUITMENT & PARTICIPANT IDENTIFICATION

We plan to use study settings and an approach to recruitment which has been highly successful in our previous trials involving the detection and intervention for people at high risk of developing more serious/long-term mental health problems e.g. psychosis (MRC funded EDIE-II trial); complex long-term mental health problems (HTA funded PRODIGY trial); bipolar disorder (BART RfPB pilot study). These previous trial experiences have provided valuable lessons regarding how to facilitate referral pathways into the BART II trial.

The approaches used previously have consisted of utilising outreach principles where participants are seen in non-stigmatising settings. This means that people often choose to be seen at home. However, other least restrictive venues e.g. youth centres, colleges, primary care settings, are also employed. Additionally, the trial will be conducted within the infrastructure of the research network as this is designed and resourced to support recruitment to large-scale studies.

To ensure the study results are readily translatable for patients within the current NHS, recruitment will involve casting our net into a variety of established services including children and young people's mental health services (CYPMHS), early intervention (EI) and detection (EDIT), community mental health teams (CMHT), increasing access to psychological treatments services (IAPT), primary care psychology services and GPs.

Recruitment will also include school/university health services and other youth services and the voluntary sector. This approach will both enhance generalisability and feasibility, given our experiences from the early detection trials and services and the pilot work which underpins this research. The aforementioned recruitment strategy fits with the research of the pathways to care often experienced by people presenting with concerns about mood swings or familial risk of bipolar disorder. Throughout the lifetime of the trial, we will document all enquiries, referrals and randomisations from each team in order to capture potential sources of bias.

Materials for advertising the study will include participant leaflets, referrer leaflets, posters, participant information sheets, and animation videos. The participant leaflets and posters were designed with our PPI group from our RfPB trial which outlines information considered to be relevant to the population in order to make decisions about whether or not to take part in the research. The animation videos will depict participation in the trial including expectations and potential risk and benefits derived from service user participant work from our RfPB trial and our newly organised SURG for this trial. In addition, we will be advertising the study on the lead site research department website and through our social media channels (BART twitter account and lead site research department instagram account). The leaflets and posters will be replicated from the RfPB study materials as these were designed at the time with a BAR Service User Reference Group and a creative designer who supported in the presentation of the information. The animation will be developed prior to the start of this trial, with the support of the newly developed SURG groups. The animations will include a specific animation for potential participants, to explain the process of taking part in the study (who the study is for, the random allocation process and what the study will involve at each time point).

Participants will be identified by a professional who is involved in their care or is known to them as being potentially eligible for the trial or will be able to self-identify. In addition to the study being advertised on social media and through the lead site research department website and similarly through other Trust sites, leaflets and posters will be displayed in settings such as waiting rooms for NHS services. The research team will be making contact and developing links with a range of mental health professionals and services (both in the

community and in the NHS setting). Developing these links will include the research team being available for brief presentations of the study, regular contact (both face to face and via electronic or telephone means) and providing training opportunities around better understanding the BAR population and what the CBT_{BAR} trial entails.

The leaflets and posters will have the contact details for who to contact in the research team when making a referral. When a referral is made, the member of the research team will conduct a brief screening check and check verbal consent to contact. Full details about the process for accepting referrals, making initial contact with a referred participant, and conducting the baseline assessment are explained in more detail in the Research Assistant Manual.

Eligibility will be confirmed with the assessor who conducted the baseline assessment and with a member of the research team based at the central site (Manchester) or with the local site lead or PI. The outcome will be recorded on an eligibility review form entered on REDCap (Research Electronic Data Capture).

CONSENT

Verbal consent to contact will be sought by a relevant professional involved in the potential participant's care (e.g. GP, university counsellor). To aid this initial discussion, all potential participants will be provided with access to the study materials described above (leaflet, animation, etc). Prior to taking written, informed consent, all potential participants will be provided with a Participant Information Sheet. This will be either given in person to the potential participant by the relevant professional involved in their care, e-mailed, or sent to them in the post. Participants will be in receipt of the PIS for at least 24 hours prior to providing written, informed consent.

Written, informed consent will be taken in person at a face-to-face appointment with the research assistant. However, in the event there are restrictions in place that prevent a face-to-face appointment (e.g. COVID-19 related restrictions) we will utilise existing approaches to taking consent remotely (approved by the sponsor including audio recording the consent appointment) and obtaining written consent when it is possible to meet face-to-face. Audio recording will be done in line with the sites NHS policy and procedures. Audio recording of consent will follow the sites local NHS Trust policies and procedures. Audio recordings will be transferred to a secure NHS drive and will only be accessible by members of the research team with delegated responsibility to access, as per the study delegation log.

***Please refer to the BART II Participant Flow Diagram found in Appendices (#1)*

PAYMENT

Participants will receive a £20 payment upon completion of the baseline and each follow-up appointment at 17-, 27-, and 52-weeks (£80 in total). In addition, a 39-week check in phone call will be conducted with each participant to confirm that contact details remain the same.

THE RANDOMISATION SCHEME

Eligibility will be confirmed via completion of the eligibility review form following the baseline assessment. This will be completed at an eligibility supervision between the research assistant and a supervisor (central site supervisor e.g. CI or trial manager, or local site lead or PI with delegated responsibility). The outcome of the eligibility review form will then need to be entered onto REDCap within 2 working days of completion of the review. If the person is eligible, randomisation will be undertaken automatically once entered in REDCap. Participants will be randomised to one of two trial arms (CBT_{BAR} + TAU **or** TAU alone). Randomisation will be independent and concealed, using permuted stratified blocks (using site and BAR Group*), via a web-based system at York Clinical Trials Unit.

**Confirmed BAR Group will be based on hierarchical rule system. Group 1 will be the stratification grouping for any participants meeting Group 1 and another BAR group (e.g. meets criteria for BAR Group 1 and 2). Group 2 will be the stratification grouping for any participants that meet BAR Group 2 and 3).*

METHOD OF IMPLEMENTING THE RANDOMISATION/ALLOCATION SEQUENCE

The allocation is made known to the trial manager (to monitor adherence to the randomisation algorithm), the local trial administrator, local PI or site lead, and local trial therapist(s) by email and SMS text message. The allocation is made known to the participant by letter from the local trial administrator. Blinding of the allocation code will be maintained for research assistants.

BLINDING

Single blind – assessors will be blind to treatment condition. Blindness will be maintained using a wide range of measures which we have implemented successfully in other single blind trials within our trust research departments. These include separate offices for the therapists and research assistants, protocols for answering telephones including reminders for clinicians, participants and family members about the blind, protocols for message taking and secretarial support, separate diaries and pigeon holes and data file security, using passwords and encryption of randomisation information.

We will develop a standard operating procedure (SOP) for maintaining, recording, and managing blinding, which will outline all of these procedures. This SOP will be reviewed by, and agreed with, our DMEC and TSC. Each researcher will sign this SOP to confirm they understand and will comply with the blinding procedures. All blind breaks will be recorded by the trial manager and reviewed by the Chief Investigator for patterns in unblindings and be reported to the TSC and DMEC. There is only one follow-up scheduled during the intervention window (at 17-weeks). This will reduce the risk of blind breaks occurring because of therapists and RAs crossing paths for visits and it will reduce the opportunity for unblinding to occur because of communication with participants to arrange visits. Our qualitative researcher WJ will be conducting interviews with participants who have received the CBT_{BAR} intervention, and this poses an unblinding risk if the RAs learn which participants met with WJ. All interviews for the qualitative research by WJ with the participants will occur at a timepoint away from a standard follow-up point and will be overseen by the trial manager to ensure participants and the RA's are not in contact.

Maintaining rater blindness to treatment allocation is crucial. Following eligibility assessment and completion of baseline assessments, participants will be allocated to treatment groups through our web-based randomisation service and the Trial administrator will inform the participants of this decision. All letters to participants and clinicians will contain a standardised statement about the need to maintain the single blinding process. Any accidental unblindings will be recorded. Where possible, we will identify an independent assessor with whom the blinding has not been broken to complete subsequent follow-ups, subject to any threats to participant engagement with follow-up.

TRIAL ASSESSMENTS

Following the recruitment process, baseline assessment and randomisation, follow-up assessment points will be at 17-, 27-, and 52-weeks post-randomisation (see "Schedule of Events" in the Appendices (#2)). We will also contact people via telephone at 39-weeks to promote retention in the trial and ask about general wellbeing since the last assessment (including documenting any potential serious adverse events, and any changes to contact details). Assessments will be conducted by research assistants blind and independent to treatment group and will employ both a semi-structured interview to gather data for the primary outcome (blinded) and secondary outcomes in addition to self-report questionnaires (unblinded data given the participant will be aware of their treatment allocation). The self-report questionnaires will be offered for completion in paper format.

For those participants who are offered the CBT_{BAR} intervention, a measure of therapeutic alliance (California Psychotherapy Alliance Scales / CALPAS) will be administered to both the participant and the therapist for completion after the 4th and 10th sessions. To ensure the participant is able to complete the measure openly, the trial manager (LP) will be responsible for contacting the participant and arranging administration of this measure to prevent the therapist being the person to do this. Additionally, the Facilitative Alliance Measure will be administered by the trial manager (LP) to the research participants following each follow-up appointment with a research assistant. This will measure alliance with the research assistant.

Follow-up visits are typically offered via face-to-face methods utilising outreach principles where participants are seen in non-stigmatising settings. This approach means that people often choose to be seen at home although other least restrictive venues e.g. youth centres, colleges, primary care settings, are also employed. Staff training will be conducted with all staff and regular arrangements for ensuring inter-reliability across sites. Adapting to assessments via phone/virtual calls still retains validity and reliability on our primary outcome [84].

QUALITATIVE RESEARCH

Nested qualitative research will examine the perceived mechanisms of change and implementation for NHS patients. After the 26-week treatment window participants will be offered the opportunity to take part in the nested qualitative study. Semi-structured interviews will explore participants' experiences of receiving CBT_{BAR} and ways in which service users perceive the mechanisms by which CBT_{BAR} causes improvements in depression and mania symptoms including key psychological processes targeted with this treatment (e.g., extreme appraisals of mood states, behaviours employed to provide coping). Additionally, interviews will seek to understand themes associated with the implementation of CBT_{BAR}.

Mechanistic objective

To determine ways in which service users perceive the mechanisms by which CBT_{BAR} causes improvements in depression and mania symptoms including key psychological processes targeted with this treatment (e.g., extreme appraisals of mood states, behaviours employed to provide coping). We will we undertake a nested qualitative study seeking to understand how participants experience or perceive the intervention to have impacted on their mood, behaviours and symptoms and draw patterns across participants' experiences. We will seek to identify components of the intervention that participants continued to utilise beyond therapy, and ways they have incorporated these into their lives. Achieving this mechanistic objective has the potential to refine and adapt the treatment model being tested within the trial.

Implementation objective:

In order to identify key themes associated with the implementation of CBT_{BAR} in NHS services we will undertake a nested qualitative study to identify potential barriers and solutions to future implementation. Key stakeholders will include service users randomised to treatment, family members, health professionals', service providers' within areas of likely service contact for the potential user (e.g. IAPT, CYPMHS, Early Intervention or At Risk Mental State teams) and commissioners. This will provide vital information to maximise the likelihood that our intervention can be delivered efficiently and effectively within the NHS after the trial has finished.

WITHDRAWAL CRITERIA

A participant is free to withdraw from the trial at any point if they wish to do so, without giving a reason and without it affecting their care. If a patient withdraws consent to participate, clarification will be sought on whether withdrawal is from the intervention component (CBT_{BAR}), and/or completing the assessments (clarifying if this includes both or either the semi-structured interviews and the self-report measures). A participant who chooses to withdraw from an intervention arm will be encouraged to continue with research assessments if they are happy to do so.

Withdrawal can also include the clinical decision by the trial therapist at site to cease or alter trial treatment, and potentially withdraw the patient from treatment. Examples of why this might be completed could include loss of capacity to consent or significant change to the person's circumstances such as significant issues with drugs or alcohol. This would be classed as "Treatment Discontinuation" on the withdrawal form. Clarification would be needed by the clinician if the research team should continue to contact the participant as normal at the follow-up points.

For those participants who take part in the nested qualitative study, they will be free to withdraw from this as well. The qualitative study will be a one-off qualitative interview; however, it could be the person initially agrees to take part but does not finish the interview. Or the person later seeks to withdraw their interview from use in the analysis.

Data collected up to the date of withdrawal of consent will be used in the analyses unless the person requests the data is not used. If necessary or helpful, an unblinded member of the research team (e.g. trial manager) will aim to have a discussion with the participant regarding their wishes.

The information about the withdrawal will be captured on a withdrawal form at site and entered onto REDCap.

If suspicion of an unacceptable risk, including serious health threat to subjects, arises during the clinical investigation, or when so instructed by the TSC / DMEC or regulatory authorities, the sponsor shall suspend the clinical investigation while the risk is assessed. The sponsor shall terminate the clinical investigation if an unacceptable risk which cannot be controlled is confirmed. The sponsor shall consider terminating or suspending the participation of a particular investigation site or investigator in the clinical investigation if monitoring or auditing identifies serious or repeated deviations on the part of an investigator. If suspension or premature termination occurs, the terminating party shall justify its decision in writing and promptly inform the other parties with whom they are in direct communication. If, for any reason, the sponsor suspends or prematurely terminates the investigation at an individual investigation site, the sponsor shall inform the responsible regulatory authority as appropriate and ensure that the TSC / DMEC is notified, either by the Chief Investigator or by the sponsor. If the suspension or premature termination was in the interest of safety the sponsor shall inform all other principal investigators.

Access to or breaking the blinding code in the case of suspension or premature termination would be decided by the independent DMEC.

END OF TRIAL

The end of trial is defined by the last visit and completion of data collection of the last participant undergoing the trial, which will be August 2025. The sponsor, or delegated individual in the study team must notify the NIHR and HRA of the end of a clinical trial within 90 days of its completion.

6. TRIAL TREATMENTS

TREATMENT CONDITION (CBT_{BAR} + TAU)

The CBT_{BAR} approach will utilise the manual used and refined in our RfPB trial. The treatment manual utilises a Cognitive Behavioural Therapy (CBT) treatment with a number of permissible interventions. An empirically tested cognitive model is required in order to derive effective treatments: this is achieved by developing an idiosyncratic formulation based on a specific cognitive model of mood swings (ICM) [57] determining treatment strategies and techniques targeting key appraisal change and coping behaviours. The ICM model used for formulation proposes that people hold a range of extreme and contradictory beliefs concerning their mood and other internal states (e.g. energy levels). For example, believing that being highly active is both the key to their success and a sign of

losing control of their mind. Owing to these beliefs, a person engages in recurrent cycles of feeling, thinking and behaviour that maintain and escalate current mood states. The therapy helps clients to identify these maintenance factors that are proposed to make their mood a problem, to learn to tolerate and accept common changes in mood, and to build up their quality of life in ways that are independent of mood state given that such attempts to control mood often get in the way of living their life goals.

The ICM model used to derive treatment targets is underpinned with empirical support from a range of research studies within clinical and non-clinical samples [57]. Studies indicate the acceptability and significant positive impact on bipolar symptoms and functioning of the therapy for people with BD [85-87]. There is also support for this model being applicable in patients with cyclothymia [88]. The model was considered appropriate for young people at risk of BD given the evidence that these appraisals are prospectively associated with bipolar symptoms, are also associated with risk or cognitive vulnerability factors for the development of BD [89], with poorer social and occupational functioning [87, 90] and distinguish BD from unipolar depression [91].

The CBT_{BAR} manual describes overarching principles of every treatment session; a positive therapeutic relationship, person centred practice and active listening and validation of experiences (taken from core principles for CBTp, [92]) and normalising and education of mood swings. Each session is delivered within the CBT model where core aspects are observed: agenda setting, review of home task, agreement on treatment goals, monitoring of target appraisals and behaviours and a new home task set. A range of permissible interventions are delivered within a 26-week treatment envelope allowing up to 26 sessions as follows:

- Mood continuum work
- Problem list generation
- Goal setting
- Idiosyncratic formulation derived from model
- In session measurement of appraisals and behaviour
- Cognitive strategies to target key appraisals of mood: advantages / disadvantages; developing alternative explanations; evidential analysis; surveys
- Behavioural strategies: behavioural experiments; behavioural analysis including intended mood management

Using this CBT_{BAR} manual in our feasibility trial showed positive results on our primary outcome of feasibility and acceptability. Inspection of the data showed that Retention to the allocated intervention was high, more specifically 32 of the 37 participants (86%) who were allocated to the CBT_{BAR} received an adequate dose (≥6 sessions) of treatment. Of the 5 participants (14%) who did not receive the dose threshold, the range of sessions attended was between 1-5 sessions. All participants met for at least 1 session. Total session numbers ranged between 1 and 26 across all participants and a grand total of 523 sessions were attended by all participants within the trial. An average of 14 sessions was attended across participants allocated to CBT_{BAR}. Although not powered to test difference between groups results indicated participants in the CBT_{BAR} arm significantly improved compared to those who received TAU alone across measures of symptoms (depressed mood) and functioning at 27-weeks with gains maintained at the 52-week follow-up. Analysis showed that risk of conversion to mania/hypomania was reduced for those randomly allocated to CBT versus TAU, although this did not reach statistical significance but it was not powered to do so (OR 27-week: 0.53, 95% CI: 0.11, 2.45, p= 0.42; OR 52-week: 0.40, 95% CI: 0.11, 1.49, p= 0.17).

The intervention will be delivered by trained psychological therapists (Senior Clinical Psychologists or Psychological Therapists) with experience of working with young adults with mental health problems, to ensure competence in engaging this population and delivering the intervention to a high standard. Trial therapists will receive training in delivering CBT_{BAR} by the study team (three days training, with two-day booster sessions in subsequent years). Additionally, therapists will make use of recording-based supervision (at a minimum frequency of each fortnight) to aid learning and practice as well as adherence to the treatment manual.

Fidelity to the treatment protocol will be assessed by rating audio recordings of therapy sessions using the Cognitive Therapy Scale - Revised (23). This is a widely-accepted approach to the standardisation of CBT, which we have used successfully in previous large-scale trials. All therapists in participating centres will be trained initially, and therapy supervision will be provided by means of regular meetings. All sessions will be taped with the patient's consent (participants may be asked to listen to the tapes as part of their homework) and a random sample of tapes (stratified for stage of therapy) will be rated in order to monitor fidelity and assist supervision; this will be done throughout the lifetime of the trial to provide some quality assurance and ensure corrective action can be taken if required. Following each session, therapists will complete a session record that monitors content of sessions in terms of agenda targets, homework tasks and change strategies used, which is another strategy we have used in previous trials; thus, fidelity can be used as a process variable in analyses.

CONTROL CONDITION (TAU ALONE)

The control condition is treatment as usual plus follow-up (17-, 27-, and 52- weeks), which represents an enhancement over routine care since symptoms of mania will be detected earlier than in usual practice and appropriate treatment referrals made. We will not be asking referrers to withhold any treatment. Participation in assessments may reduce the (frequently high) number of contacts required in order to receive appropriate treatment for BD. Assessments will identify untreated BD and any risks to self or others that require immediate action. TAU alone will not include liaison with a clinical team, should one be involved, except where risk issues necessitate this. This is a pragmatic approach that will improve generalisability of our findings. As in previous trials we have undertaken, there will be a clear safety protocol to alert clinicians should suicidal or dangerous ideation emerge, and an operational protocol for initiating high quality routine care should conversion occur.

Treatment as usual will include standard psychiatric care, psychological and vocational interventions from a variety of agencies will be available to both treatment and control arms (although, in our experience, provision for this population is poor). Due to diagnostic uncertainty, access to services includes Improving Access to Psychological Therapies (IAPT), CAMHS, primary care, EIT and community mental health teams. CBT_{BAR} differs from standard NHS treatment for young people with mood swings as highlighted in our RfPB trial [59]. All routine or additional treatments in both conditions will be monitored using a Treatment Documentation Sheet and specific treatments (anti-depressant and psychotherapy treatment) monitored within the LIFE assessment tool as important potential confounders.

CONCOMITANT THERAPY

It would be unethical to restrict the therapeutic options of the young people participating. Our approach will, therefore, be primarily to record the use of all other medication and psychological therapies, document details of dosage, and ensure the follow-up of all randomised participants, irrespective of the interventions that they subsequently receive.

We will collect participant self-report on the use of medication and psychological therapies (including CBT or CBT informed treatments). All participants will be eligible to receive medications (other than mood stabilisers for longer than 6-weeks or antipsychotics for longer than 3-weeks at baseline) as well as psychological interventions.

ASSESSMENT OF ADHERENCE TO TREATMENT

Four related aspects will be monitored and assessed: (i) participants' adherence to the therapy; (ii) therapist competence (iii) therapist adherence to the manual (iv) overall therapy fidelity.
Participants' adherence to the therapy will be assessed by recording the number of sessions offered and attended, including length of sessions attended, and completion of between-sessions tasks (therapy 'homeworks').

Therapist competence and adherence to the manual will be monitored through recordings of therapy sessions, with participants' consent. This is a widely accepted approach to the standardisation of psychological therapies. Therapists will have weekly supervision from a senior clinical psychologist from the central team, who will listen

to and provide detailed feedback on a selection of therapy tapes, with participants' consent, on a weekly basis, to ensure competence and adherence. All therapists and supervisors will also meet remotely with the research team therapy leads for monthly group supervision. This will be done throughout the therapy delivery period to provide quality assurance and ensure action can be taken if required.

Therapy tapes from five participants on each site (total of 25 participants) will be randomly chosen, with participants' consent, to be rated by a clinician independent from the trial, to provide an objective verification of therapist competence and adherence to the manual. Therapist competence will be rated using an existing measure assessing skills and competences related to delivering CBT [93] in line with national programmes and treatment trials utilising CBT models. A rating form for therapist adherence to the manual will be utilised and will consist of a list of therapeutic procedures extracted from the CBT_{BAR} treatment protocol.

To assess overall therapy fidelity, following each session, therapists will complete a checklist to record content of sessions in terms of agenda targets, homework tasks and change strategies used. These data will be extracted at regular time points throughout the trial to check therapy milestones are being met and ensure the therapy protocol is being followed. This ongoing monitoring will pick up on any fidelity issues across sites or individual therapists and will inform training and supervision content.

STUDY PARTICIPANT SUPPORT

We will attempt to ensure that treatment as usual conforms to ethical practice and is standardised to some extent by the provision of 3 additional components – ensuring registration with a GP, a suicide risk management plan where relevant and a crisis card for participants. Crisis cards will include helplines which may be national or local numbers (specific for each site) useful for this group. All participants will be offered a standardised telephone contact within 48 hours of assessments. Participants will not be denied any existing service in either arm of the trial. In both arms, they will be encouraged to engage in and continue with existing treatments. Standard psychiatric care, psychological and vocational interventions from a variety of agencies will also be available to both treatment and control arms (although, in our experience, provision for this population is poor). All study participants will be provided with contact details for the researchers and principal investigator of the study so the potential participant can contact research staff to ask any questions or discuss any concerns they might have about their participation.

7. (Serious) Adverse Events

For the purpose of recording and reporting (Serious) Adverse Events for this trial, the GMMH (sponsor) Standard Operating Procedure (RD2OP41 Recording and Reporting Adverse Events for non-CTIMPS) will be followed.

DEFINITION OF ADVERSE EVENTS (AE's)

Any untoward medical or psychological occurrence in a patient or trial participant receiving psychological therapy or other trial intervention and which does not necessarily have a causal relationship with this intervention. An adverse event can therefore be any unfavourable and unintended sign, symptom, or disease in any subject in a trial (including those in an untreated control group), whether considered related to the investigational psychological therapy/intervention.

As well as broadly defined 'medical events' including self-harm and worsening of symptoms which were absent or present at baseline, adverse event recording will also include capturing information about the occurrence of non-medical events such as arrest, imprisonment, and violence to others, which may be contributing factors to an AE or may indicate that an AE has occurred. As an example of the latter, a participant's increased drug abuse—an AE—could result in an arrest.

DEFINITION OF SERIOUS ADVERSE EVENTS (SAE's)

Any untoward medical or psychological occurrence that:

- Results in death
- Is life-threatening (NOTE: this refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalisation or prolongation of existing hospitalisation (We plan to scrutinise any instances of patients being admitted to psychiatric hospital in the period of the therapy. These events are likely to come to the attention of the therapists or assessors)
- Results in persistent or significant disability / incapacity
- Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences plus any serious violent incidents or formal complaints about the intervention.

NB: Planned hospitalisation for a pre-existing condition, without a serious deterioration in health, is not considered a serious adverse event.

REPORTING PROCEDURES FOR ADVERSE EVENTS

For the avoidance of doubt, all AE/SAEs should be collected for all trial subjects from the time of their enrolment into the study. The time of enrolment is defined as the time at which, following recruitment, a subject sign and dates the informed consent form. Initially all adverse events should be recorded on the Adverse Events Report Form by whoever has identified the event. This form should then be shared with the Chief Investigator (Sophie Parker) or trial manager (Lydia Pearson) who makes an assessment as to whether the event is defined as serious in consultation with both the definitions in the Protocol and the GMMH SOP (RD2OP41 Recording and Reporting Adverse Events for non-CTIMPS). The response to an adverse incident will be determined on a case-by-case basis and in line with HRA guidance. The recorded AE's will be regularly monitored by the trial management group in line with Good Clinical Practice Guidelines.

REPORTING PROCEDURES FOR SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) occurring to a participant will be reported to the following agencies and committees using the HRA report of serious adverse event form (see HRA website):

- To the sponsor, no later than 3 calendar days from awareness of the event at the site.
- The REC that gave a favourable opinion of the study The DMC who will be responsible for reviewing serious, unexpected and related events
- Additionally, all SAE's will be reported to the responsible clinical team and the TSC.
- Finally, details of all serious and non-serious adverse events will be reported externally to the funder in regular progress reports.

8. STATISTICS & DATA ANALYSIS

MAIN TRIAL DATA ANALYSIS

All comparative analyses will be 'as randomised', where participants are analysed according to the group they were randomised to, regardless of what treatment they received. Complete details of analyses will be included in a Statistical Analysis Plan which will be finalised and approved by the Trial Steering Committee prior to database lock and prior to any analysis.

Co-primary outcomes

The primary analyses for each of the co-primary outcomes (mean 4-week PSR for LIFE depression score and for LIFE mania score at 27-week follow-up) will use ANCOVA, with adjustment for the stratification factors (site and BAR group) and the baseline PSRs for depression and mania and prior CBT (yes/no). Missing data will be explored; for each co-primary, if less than 15% are missing, and less than 10% differential missing data, then case analysis (CCA) will be used, otherwise it will be multiple imputation by chained equations (MICE) [94] assuming that the data are 'missing at random'. Tests will use a 2.5% significance level and two-sided 97.5% confidence intervals (CIs) will be presented.

Moderator: We will explore BAR group (I, II or II) and prior CBT (yes; no) as potential moderators by adding interactions with treatment arm to the primary outcome models.

Mechanisms: We will evaluate this using causal inference methods for mediation [95] using an instrumental variables approach (via two-stage least squares) to estimate the indirect effect of CBT_{BAR} on each of LIFE mania and LIFE depression scores via the HAPPI total score at the preceding time-point (e.g. 17-week HAPPI for 27-week LIFE scores). The more complex causal model incorporating BC and ISS will be investigated using structural equation modelling. As a post-randomisation effect modifier, the impact of the number of CBT_{BAR} sessions attended will be assessed using principal stratification methods; other measures of intervention receipt, including antidepressant medication, will be considered in separate analyses.

Secondary outcomes

Secondary outcome measures (including the primary outcome measures at time-points other than 27-week) will be analysed using generalised linear models, with link function appropriate to the type of data, adjusted for stratification factors and the baseline value of the outcome measure (where applicable).Time to events (transition to first episode (hypo)mania and recovery from BAR symptoms) will be analysed using a Cox proportional hazards model, adjusted for stratification factors. Tests will use a 5% significance level and two-sided 95% CIs will be presented.

Sensitivity analysis

The alternative method to that used in the primary analysis will be used as a sensitivity analysis (MICE if CCA, or vice versa). Sensitivity analyses will also include the addition of a random therapist effect in a partially-nested model (clustering by therapist in the CBT_{BAR} + TAU arm but no clustering in the TAU arm). A further sensitivity analysis will use longitudinal mixed-effects model incorporating all follow-up time-points (as factors), fitted using maximum likelihood, accommodating the within-participant correlation over time with an unstructured covariance matrix and including stratification factors and the baseline PSRs for depression and mania as covariates.

QUALITATIVE ANALYSIS

Data will be analysed using thematic analysis [96], which provides an accessible and flexible approach, resulting in a rich account of qualitative data. The data generation and analysis will be conducted with leadership and ongoing involvement from individuals with personal experience of the provision of the receipt of this treatment and/or the experience of BAR mood experiences. This involvement is expected to enhance the study during the conduct and analysis of all interviews. We will take a critical realist position, and data will be coded at a manifest level (i.e., analysing only the immediate meaning of participants' language) to produce an accessible body of coded data from which meaningful thematic representations of participants' perspectives can be reported. All semi-structured interviews will be transcribed verbatim and coded systematically and iteratively within NVivo qualitative data analysis software (Version 11, 2016).

In order to achieve our objectives to explore mechanisms, participant interviews will be analysed to investigate the mechanisms by which the intervention is perceived to operate. Here we will employ an inductive approach whereby the researchers will not impose a pre-existing theoretical framework but will seek to identify and code

data that offer relevant information about how participants experience or perceive the intervention to have impacted on their mood, behaviours and symptoms and draw patterns across participants' experiences. The analysis will be conducted by qualitative researchers with lived experience and will follow the steps of Braun and Clarke [97]. Regular analysis meetings with the wider multidisciplinary research team which leads to further develop emerging thematic and conceptual outputs.

In order to explore implementation, stakeholder interviews will also be analysed inductively following the 7 steps of Braun and Clarke's approach, to examine the potential barriers and solutions to implementing the intervention into routine care and services. Regular analysis meetings will be key, not only to support the development of the emerging analysis, but also to ensure that valued that may be relevant to trial participant recruitment, are transmitted to the teams as a whole as quickly as possible Member checking will be conducted to ensure the trustworthiness of the final analysis [98].

9. DATA MANAGEMENT

Data management will ensure each study participant is assigned a unique trial identification number at the start of assessments and written on all clinical assessment forms/datasheets and databases used to record data on study participants. A record sheet linking patient identity, contact details and trial identification number for all participants is kept at each site. It will be placed securely in a locked filling cabinet separate from datasheets. This will be stored in an electronic database, accessible only to authorised users at the sites via the study web portal hosted at York CTU (password protected and secure). The local study co-ordinator will enter the data on to a REDCap Cloud database, and managed and subject to quality control according to MCTU procedures by MCTU.

Data will be held securely on a cloud-hosted REDCap server. Access to the study interface will be restricted to named authorised individuals granted user rights by a REDCap administrator at York CTU. All data will be kept secure at all times and maintained in accordance with the requirements of GDPR and archived according to GCP regulations. Paper data collection forms transferred to or from the York Clinical Trials Unit will be coded with a study number, the participant's initials, and date of birth. Data will be held securely on paper and electronically at York Clinical Trials Unit and appropriate processes put in place for the transfer, storage, restricted access, and disposal of personal information. Relevant Standard Operating Procedures, Guidelines, and Work Instructions in relation to data management, processing, and analysis of data will be followed.

Participating sites will be expected to maintain a file of essential trial documentation (Investigator Site File), which will be provided by GMMH and keep copies of all completed paper assessment packs and consent forms for the trial securely.

10. MONITORING, AUDIT & INSPECTION

Each site will have a weekly team meeting to ensure regular communication and interaction between site leads, local clinicians and research assistants (with measures to maintain the blind). Monthly Trial Management Group meetings with all applicants via video conference will occur, with 6 monthly extended meetings. LP will conduct weekly telephone supervision with all RAs focusing on recruitment, liaison with referrers, compliance to follow-ups, and specific scoring queries for interview-based measures. In addition, LP will chair a fortnightly teleconference focusing on inter-rater reliability of the interview measure and recruitment to share best practice. Therapists receive weekly site supervision from a central supervisor based in Manchester, focused on fidelity and adherence to the protocol and manual. Line management / supervision from site leads focussed on problem solving, personal wellbeing, risk management and local issues will supplement this. Quarterly triadic site supervision involving supervisee, central supervisor and site leads will be used to ensure these

arrangements operate smoothly. We have used these processes successfully in several previous multisite RCTs of psychosocial interventions [99, 100].

Data will be monitored for completeness by the research assistants at the end of each visit. Researchers may also contact participants by telephone or e-mail to facilitate data completion where appropriate.

11. ETHICAL & REGULATORY CONSIDERATIONS

RISKS, BENEFITS AND BURDENS

Some participants may find completing some of the assessments distressing. To minimise this, participants will be offered choice regarding the length of the assessments, including the option of breaks and completing the assessments across multiple sessions. We have a standardised protocol for managing distress that has been developed with our local research department's Service User Reference Group (SURG). The protocol includes providing a crisis card listing relevant phone numbers and offering standardised telephone contact within 48 hours of assessments. In addition, if a participant begins to show signs of distress during an assessment the researcher will discuss this with the participant, have a break or stop the assessment. With the participants consent the researcher will also liaise with a relevant health professional involved in the participant's care (e.g. they could attend the initial assessment to help the participant feel more comfortable, or if the participant wishes the research to do so they can inform the relevant health professional of the distress reported). Furthermore, the researcher will gain advice from their supervisor and take any appropriate action to minimise the participant's distress. The participant will be able to freely withdraw from the study at any point, which will also be clear on the consent form and this will not affect their statutory care.

CONFIDENTIALITY

All the information that is collected about participants will be strictly confidential. However, all participants will be made aware through the Participant Information Sheet and verbally by Research Assistants and Therapists that although their data is strictly confidential, this confidentiality can be broken if they are deemed a risk to themselves or others. Where a participant is deemed to be a risk to themselves or others or where risk to the participant from someone else is identified an appropriate plan will be implemented e.g. a suicide risk management plan, and actions taken by the researcher to ensure their safety. This will include reporting these concerns to the clinical team (via encrypted email or phonecall as per local policy) or making a referral to an appropriate service, ensuring that these concerns are documented within the clinical record, raising any safeguarding referrals and following any other local Trust policies required. If concerns regarding risk to self or others is present, then the research blind might have to be broken to ensure that all the research team are fully aware of the risks.

12. DISSEMINATION POLICY

A number of outputs are expected from the research. This research will provide data to support development of an evidence-based treatment for young people meeting BAR criteria deliverable within the NHS. This will address the unmet need within this population in order to understand the expansion of youth service models to widen intake criteria to encompass BAR. Specifically, this will provide valuable data on how CBT_{BAR} impacts on the pathway between key psychological processes and mood swings as a reduction of risk to long-term distressing mood swings. This can inform plans to provide access to evidence-based treatments through NHS services by 2023 to 2024 [53] & NHS Mental Health Implementation Plan [54].

We will publish a number of high impact peer reviewed journals: study protocol (independent of results) will be submitted to BMC psychiatry; results for the primary and secondary outcome measures for the main trial will be submitted to Lancet Psychiatry and Efficacy and Mechanism Evaluation journal; psychological mechanisms work. The qualitative results will be targeted as 3 papers regarding the acceptability of the approach with a more diverse population (PAPTRAP), the perceived mechanisms of change (PlosONE) and the implementation of CBT_{BAR} from key stakeholders (British Journal of Psychiatry). Our quantitative data may be of interest to researchers examining the efficacy of psychosocial interventions in Bipolar at Risk, e.g. for systematic review and meta-analyses, individual patient data analysis and will be made freely available.

A number of conferences will be attended in order to disseminate the findings of our approach. Conferences attended by CYPMHS staff, those working within EI and CBT practitioners will be of most benefit. We will ensure as many opportunities as possible to deliver such talks alongside our PPI co-applicants and SURG members. We will seek to present our research to important voluntary sector service / service user networks e.g. Bipolar UK, Moodswings Network. Dissemination to participants, families, health professionals and key stakeholders will be enhanced by our ongoing PPI work. Our PPI group will help develop dissemination materials that will include an animation. This animation is derived from illustrations from our feasibility trial and will be built on to capture the story of what taking part in the trial was like, what the therapy was like, and participants' perceived mechanisms of change were. We will seek to work within our established national networks to disseminate findings from this research across a range of key stakeholders. Our qualitative work on implementation questions will recruit participants across the range of key stakeholders and will include commissioners, service providers/leads, clinicians and service users. We will utilise this strand of work to understand more about the potential barriers and solutions to the dissemination of this work and anticipate engaging with a number of service providers in order to disseminate results. We will employ and train NHS clinicians to deliver treatments which provides an immediate dissemination of this approach with their employing organisations. In addition, we have a strong track record of dissemination and implementation, which has been achieved through a systematic approach of delivering clinical workshops and training events.

Impact from this research will be achieved in several ways. Firstly, to the group of participants and their families who take part in the research, our RfPB trial reported benefits from trial participation regardless of randomisation outcome. Additional benefits are anticipated to those who get randomised to receive CBT_{BAR}. This will have immediate impact on 169 NHS patients. We will ensure the provision of our CBT_{BAR} manual plus training materials, which will facilitate effective uptake, implementation and sustainability in the NHS. This will be supported through the continued support from our links with TrustTech. No intellectual property barriers are anticipated.

In line with the work we conducted during the feasibility trial and on similar research projects within our department, we will undertake a number of activities to keep our participants informed of progress and findings of the research including: Bi-annual newsletter; Social media presence; Webpage; Participant feedback day; Animation of mechanisms developed collaboratively with PPI group.

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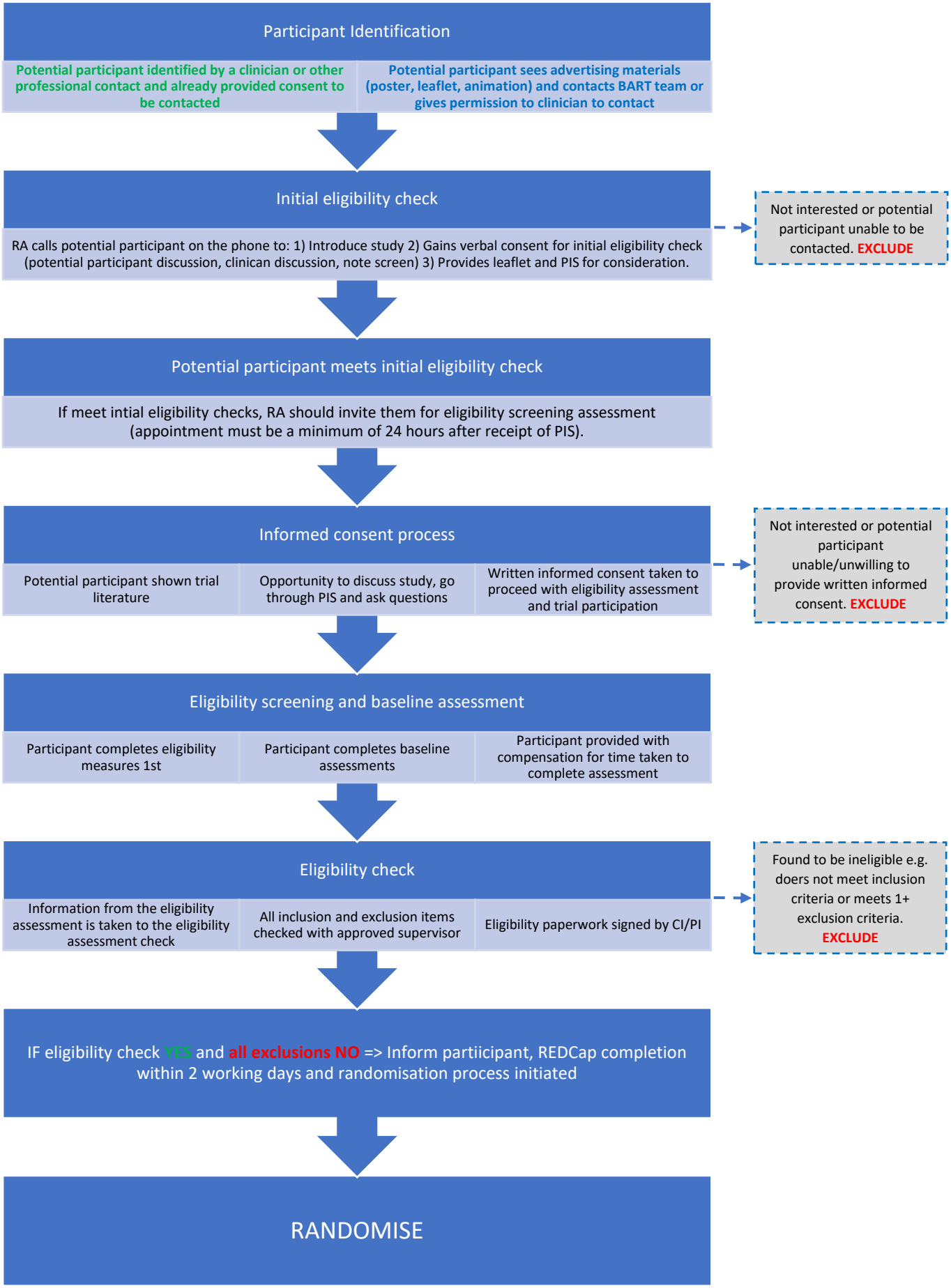
14. APPENDICES

1. BART II Participant Flow Diagram
2. Schedule of Events

Appendix 1. BART II Participant Flow Diagram



Appendix 2: Schedule of Events

Procedures		Eligibility and Baseline Assessment (Day –28 to –1)	Day 0	Intervention 1, week 1	Weekly session, ≤26 sessions CBT_{BAR}									Intervention 26, week 26	Study Visit 1 (week 17)	Study Visit 2 (week 27)	Study Phone call (week 39)	Study Visit 2 (week 52) Study Completion
Signed Consent Form		X																
Demographics		X																
Assessment of Eligibility Criteria: SCID-5 + PSR's (SCID LIFE), GAF/SOFAS		X																
Baseline Assessment Completion: ISS, BDI-II, HAPPI, BC, BCSS, MCQ-30, DTQ, RSQ, EQ-5D, WHOQOL (PSQI/PANSAM?)		X																
Allocation / Randomisation			X															
Interventions	CBT_{BAR} (including sessional measures: ISS, HAPPI, BC)			X	XXXXXXXXXXXXXXXXXXXXXXXXX ≤26 sessions CBT_{BAR}									X				
	Treatment As Usual (TAU) Alone (**not a study procedure, TAU provided by clinical team*)				◆								◆					
Alliance	Therapist Alliance: CBT_{BAR} only				X			X										
	Research Assistant Alliance	X													X(?)	X(?)		X(?)
Adverse Event Recording				X	X	X	X	X	X	X	X	X	X	X	X	X		X
Contact sheet update																	X	
Assessment of mechanism: HAPPI, BC, ISS		X													X	X		X
Assessment of Outcome	Mental Health Experiences															X		X
	Psychological Process Measurement															X		X
	Quality of Life/Functioning															X		X
	Service Use Interview															X		X